Chapter Two

Background

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April 3, 1998

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I. Endocrine Disruption: An Overview of the Issue

A. The Endocrine System

B. How the Issue of Endocrine Disruptors Evolved

[NOTE TO THE READER: The EDSTAC plans to include text that addresses the two topics listed above. When completed, the text is intended to provide background information to help the reader understand some of the basic features of the endocrine system and how the issue of endocrine disruptors evolved up to the point of the formation of the EDSTAC.]

II. Statutory Basis for Endocrine Disruptor Screening and Testing

A. FQPA and SDWA Endocrine Disruptor Screening and Testing Provisions

As noted above, the 1996 Food Quality Protection Act (FQPA) and the 1996 Amendments to the Safe Drinking Water Act (SWDA) require the U.S. Environmental Protection Agency (EPA) to:

> *"develop a screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as the Administrator may designate."*

The laws required the EPA to develop a screening program by August 1998; to implement the program by August 1999; and to report on the program's progress by August 2000.

The two laws target different sets of chemical substances. Section 304 of the FQPA states that in carrying out the program, the Administrator shall:

> *"(A) provide for the testing of all pesticide chemicals; and (B) may provide for the testing of any other substance that may have an effect that is cumulative to an effect of a pesticide chemical if the Administrator determines that a substantial population may be exposed to such a substance."*

Section 136 of the Safe Drinking Water Act Amendments states that:

> *"in addition to the substances referred to in (FQPA), the Administrator may provide for testing under the screening program authorized by (FQPA) for any other substance that may be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance"*

B. Additional Chemical Screening and Testing Authorities

The FQPA and SDWA did not arise in a vacuum. Rather, the FQPA and SDWA requirements for endocrine disruptor screening and testing place another layer of screening and testing activity on an already extensive regulatory system to which new and existing pesticide and industrial chemicals are already subjected. These include:

- Federal Food, Drug and Cosmetic Act (1938) as amended (1958) -- As it applies to EPA, FFDCA regulates the use of pesticides as food-additives. Pesticide tolerances for food are established under this Act. A tolerance is the maximum amount of residue allowed to remain on an agricultural commodity at the time of harvest.

x

- Federal Insecticide, Fungicide and Rodenticide Act (1947) as amended -- FIFRA provides a regulatory framework for the registration and use of pesticides.

x

- Clean Water Act (Federal Water Pollution Control Act, 1972 as amended) -- The CWA regulates toxic water pollutants.

x

- Safe Drinking Water Act (1974) -- The SDWA sets enforceable standards for substances in drinking water.

x

- Toxic Substances Control Act (1976) -- TSCA requires notification before new chemicals can be placed into the commerce and gives authority for testing, information reporting and for controlling new and existing industrial chemicals.

C. Scope of the EDSTAC

In convening the EDSTAC, EPA did not limit the Committee to the narrow set of chemicals and the single hormonal system explicitly mentioned in the FQPA and SDWA endocrine disruptor screening and testing provisions. Nor did the EDSTAC limit its recommendations to the protection of human health. Rather, as described more fully in Chapter Three, the EDSTAC strongly recommends that EPA's endocrine disruptor screening and testing program should:

- address both human health and ecological effects;

- initially emphasize identifying and characterizing effects that enhance, mimic, or inhibit estrogenic-, androgenic-, and thyroid hormone-related processes; and,

- be capable of evaluating the endocrine disrupting properties of both chemical substances and common mixtures.

The EDSTAC believes that this scope properly reflects a broad concern about the potential human health and ecological effects of endocrine disruption~~, as well as the broad testing and regulatory authorities available to EPA~~. Given the recommended scope of the program, the EDSTAC discussed additional testing authorities. ~~focused its attention on the statutes which provide the statutory basis for endocrine disruptor screening and testing.~~ These included FIFRA and FFDCA (as amended in FQPA), TSCA and SDWA. An overview of FQPA and TSCA is provided below. A very brief summary of other key components of the FQPA is also provided. These overviews are provided for information purposes only. They do not represent any interpretation of statutory authority by either EDSTAC or EPA.

1. Other Key FQPA Provisions

The FQPA revised the Federal Food, Drug and Cosmetic Act (FFDCA) and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The major FQPA amendments to the FFDCA include: 1) health based safety standards for pesticide residues in food; 2) special provisions for infants and children; 3) limits on "benefits" considerations; 4) review of all existing pesticide tolerances by the year 2006; 5) uniformity of tolerances; and, 6) screening and testing for endocrine disruptors. Specific FQPA amendments to FIFRA include: 1) pesticide re-registration is required every 15 years; 2) EPA is required to develop procedures for expedited review of safer pesticides; 3) provisions to facilitate “minor use" registrations; and, 4) requires EPA to expedite the review and registration of anti-microbial pesticides.

2. FIFRA Testing Provisions and Universe of Chemicals

Under FIFRA, EPA regulates pesticides which includes insecticides, herbicides, fungicides, rodenticides, disinfectants, plant growth regulators, biological agents, and other pest control agents. FIFRA gives EPA the authority to register pesticides to ensure no unreasonable adverse effects to human health or the environment, taking into account the economic, social, and environmental costs and benefits of the pesticide use. As such, FIFRA is a cost-benefit statute. In other words, the determination of what constitutes an “unreasonable adverse effect” must

account for socioeconomic factors as well as scientific judgments. The primary regulatory vehicle under FIFRA is the pesticide label ("the label is the law"). Every registered pesticide product must bear a label that includes the producer number, product registration number, active ingredient statement, warning or precautionary statements, and directions for use.

Registration and re-registration decisions are based in part on the evaluation, synthesis, and integration of pesticide studies conducted by registrants and others and submitted to the Agency. The data requirements and the Agency's ability to require special studies when deemed necessary are substantial. Studies are routinely conducted in mammalian toxicology, occupational and residential exposure, residue chemistry, environmental fate and transport, and ecological effects. Individual studies are evaluated by EPA scientists, and subsequently used in human health and ecological risk assessments. The risk assessments are then used by regulatory decision-makers who make the final risk management decisions.

Until FQPA was passed, risk assessments for pesticide registration characterized estimates of risk only for single active ingredients. Dietary risk assessments included an estimate of risk from all use-sites (e.g., corn, cotton, wheat, ornamental plants, etc.), but non-dietary (e.g. occupational or residential) risk assessments addressed each exposure scenario separately. Ecological risk assessments are addressed at only single sites as well. The scope and complexity of any specific pesticide risk assessment varies with the specific chemical and use pattern(s), but a tiered, iterative approach is commonplace. For human health assessments, worse case assumptions are applied as estimates of exposure. If the risk estimate exceeds the level on concern, additional empirical or surrogate data are used to refine the exposure assessment, until such time as it can be shown that the level of concern is not really exceeded, or the decision is made that risk reduction measures should be taken. For ecological assessments, the tiers progress through simple risk quotients derived from laboratory fate, transport, and toxicity data in early tiers, to a weight-of-the-evidence approach in later tiers.

When a pesticide undergoes evaluation for registration, reregistration or Special Review, the scientific disciplines review and evaluate registrant-submitted and other studies in a comprehensive manner to ensure they meet scientific and regulatory policy standards established for carrying out risk assessments. The studies are evaluated and integrated in such a manner that routes of dissipation, significant environmental degradates, residue levels and residence time of persistent degradates in the various environmental compartments are elucidated. This information along with the hazard profile of the pesticide, as determined in the required studies and available incident data, is used to determine risk in aquatic and terrestrial environmental compartments. If a high level of concern is identified, risk mitigation options are identified and considered for

inclusion on the pesticide label. If the available options are not adequate to reduce the level of concern to an acceptable level, the use may not be approved or may be rescinded.

EPA's Office of Pesticide Programs currently reviews about 5,000 pesticide registration submissions annually. The scope of the submissions ranges from simple label amendments to registration of new active ingredients. Since 1947, thousands of pesticide products have been registered. Perhaps not surprisingly, standards for approval and test data requirements reflect changes in science and pesticide regulatory policy over time. To ensure compliance with current scientific and regulatory standards, FIFRA now requires the review and re-registration of existing pesticides every 15 years. At any time, registrants may delete pesticide uses or voluntarily withdraw products or uses that are not economically feasible to maintain. Further, EPA has the authority to cancel registrations for pesticide products that do not meet the requirements for re-registration (or registration, for that matter). The number of registered products subjected to re-registration in response to the 1988 amendments to FIFRA was approximately 50,000. The total number of products remaining on the market is now about 20,000.

Presently, there are approximately 600 registered pesticide active ingredients, and 1800 inert ingredients. Inert ingredients used in pesticide formulations are subjected to test requirements that are less comprehensive than those for active ingredients. Under the FQPA screening and testing program, both active and inert ingredients are to be included. Many of the pesticide "inerts" are also listed in the TSCA Inventory, which is described below, as are a number of the active ingredients (because they also have non-pesticidal uses).

In the registration or re-registration process, problems that arise during the review of a particular pesticide may be investigated under the Special Review Process. Special Review is a formal scientific and legal process in which EPA presents its case that the use(s) of a currently-registered pesticide may be presenting risks of concern, and, thus, risk reduction or cancellation of the use(s) may be warranted. Special Review is conducted by notice and comment rulemaking. The science issues are developed and must be presented to the FIFRA Scientific Advisory Panel for review. Additionally, the U.S. Food and Drug Administration, the U.S. Department of Agriculture and congressional committees are invited to provide formal comments. Once a decision is made, the registrant may appeal the decision through administrative procedure or judicial review.

The FQPA amendments to FIFRA require EPA to reassess all existing pesticide tolerances of food use pesticides by the end of the year 2006. The data requirements for pesticide registration are substantial, and the burden of proof to demonstrate safety lies with the registrant. As such, the EPA has significant authority to issue a "data-call-in" requiring the registrant to conduct

studies to rebut a presumption of risk identified by EPA. Nevertheless, the data bases for any given pesticide may vary substantially. The types and minimum amounts of data that registrants are required to submit or cite in support of an application are listed in 40 CFR Part 158. The data requirements vary according to use patterns (e.g., terrestrial food crop, indoor domestic, etc.) and physicochemical properties (e.g., gas, volatile liquid, dust, chemical class, etc.). As such, for purposes of priority setting, it is important that each pesticide be critically examined on a case-by-case basis with respect to the adequacy of existing data for the evaluation of endpoints due to endocrine disruption, as well as exposure potential.

3. TSCA Testing Provisions and Universe of Chemicals

TSCA was signed into law in 1976 and most of its provisions became effective on January 1, 1977. TSCA requires EPA to "compile, keep current, and publish a list of each chemical substance which is manufactured or processed in the United States." TSCA exempts chemicals used only in small quantities (as defined by EPA by rule) for research purposes from this listing.

Chemical regulation under TSCA is quite different than that described above for FIFRA. Under the New Chemical Review Program, manufacturers must submit Pre-Manufacture Notification (PMN) for new chemicals. By statute, EPA must review the submission within 90 days. Because there is no obligation on the part of the manufacturer to develop toxicity data prior to notification, the main tools the Agency uses in this review are Structure-Activity Relationship (SAR) models. In practice, EPA often drops review and gives approval for most chemicals. Where appropriate, the Agency prohibits or limits manufacture, processing, distribution, use or disposal when it judges the chemical may present an unreasonable risk and data are inadequate. The Agency can require testing for chemicals that will have substantial production, significant exposure, or substantial release. Testing may also be required for chemicals that pose significant risk. Testing is tied to affordability.

Testing of existing chemicals under TCSA is conducted differently than for new chemicals. Test requirements for existing chemicals are determined by a rule-making or through a negotiated Enforceable Consent Agreement (ECA). To require testing of existing chemicals the Agency must make a finding that the chemical may present an unreasonable risk to human health or the environment or, alternatively, that it is produced in substantial quantities and there is substantial or significant human exposure or substantial environmental release. These findings which EPA makes under TSCA 4(a)(1)(A) and 4(a)(1)(B) are discussed in the following paragraph. In addition, EPA must find that there are inadequate data to reasonably determine or predict the effects of the chemical on human health or the environment; and that testing is necessary. This

testing may include health effects, environmental effects, chemical fate in the environment, and exposure.

Under TSCA Section 4(a)(1)(A), EPA must have a suggestion of hazard and there must be an exposure to the chemical for EPA to require testing data. Under TSCA Section 4(a)(1)(B) data may be required when there is: substantial production (one million pounds per year threshold value); and a) substantial release (the lessor of one million pounds per year or 10% of production); b) substantial human exposure (widespread human exposure indicated by 1,000 workers, 10,000 consumers, 100,000 members of the general population); or, c) significant human exposure under special high exposure scenarios.

EPA's initial listing of chemicals in commerce, commonly called the "Initial Inventory" or the "1977 Inventory," consisted of those chemicals that were manufactured in the U.S. or imported into the U.S. on or after January 1, 1975 and before the end of the initial reporting period (this period varied depending on the chemical/company circumstances and certain allowances were made for later additions and corrections). The Initial Inventory was published in 1979 and contained about 60,000 chemicals. This represented the initial set of "existing chemicals" and the basis for distinguishing between "new" and "existing" chemicals under TSCA. Chemicals not on the Inventory are considered "new" and are subject to the PMN requirements of TSCA. After EPA completes the pre-manufacture review of a new chemical and when the manufacturer or importer of the chemical notifies the Agency that manufacture or importation has commenced, EPA adds the new chemical to the Inventory.

As of August 18, 1997, based on a search performed by EPA for the EDSTAC, there were about 75,500 chemicals in the TSCA Inventory. Of the 75,500 chemicals, 2,643 are inorganics, 24,160 are polymers, 48,697 are organics, and about 500 are complex substances from petroleum refining streams. The "metals" are distributed among the inorganics, polymers and organics.

At the time the Initial Inventory was compiled, production data were also collected for those chemicals. Production data have been updated three times for a subset of Inventory chemicals. The Inventory Update Rule (IUR) has required reporting of the quantities of subject chemicals produced in 1985, 1989, and 1993. Categories of chemicals exempted from IUR reporting are polymers, inorganics, microorganisms, and naturally occurring substances. Additionally, the IUR has a reporting threshold of 10,000 lbs per site for each chemical, i.e. reporting is required for a chemical only if a company manufactured or imported at least 10,000 lbs of the chemical at any single site during the year covered by the rule. Of the organics, about 12,340 have been produced or imported in excess of 10,000 pounds in 1985, 1989 or 1993. Of these about 11,037 are

organics that are non-petroleum fractions. Available recent production or importation data on inorganics or polymers are not easily accessible.

EPA estimates that a total of about 15,000 non-polymeric chemicals are manufactured or imported at levels above 10,000 pounds per year (the 12,000 IUR chemicals plus an estimated 3,000 chemicals from exempt categories (primarily inorganics)). Within this set of 15,000 non-polymeric chemicals, there are about 3,000 chemicals produced in amounts over 1 million pounds per year. About 25,000 chemicals potentially subject to the IUR have never been reported on the IUR, indicating that they are manufactured or imported in amounts less than 10,000 pounds per year and, in some cases, may no longer be produced at all.

Although EPA has authority to order testing of chemicals under TSCA, in the nearly 20 years of TSCA's existence, this authority has been used for only 121 chemicals. This is not an indication of how much more information might really be needed but, rather, the administrative challenges of mounting an information request. Because of the expense in justifying and preparing test rules, and concern over litigation, EPA tends to rely on negotiated consent orders and voluntary testing which have resulted in testing of an additional 443 chemicals.

4. Relevance of the FFDCA and Universe of Chemicals

In addition to the chemicals regulated by EPA under TSCA, FIFRA and FFDCA, there are a large number of chemicals that are regulated under FFDCA and other statutes by other agencies that may present significant exposures to humans and for which there are essentially no data on the potential for endocrine disruption. The EDSTAC is recommending that ingredients in cosmetics, food additives (including those Generally Regarded As Safe - GRAS, under the FFDCA), and nutritional supplements also receive serious consideration for priority setting within the endocrine disruptor screening and testing program. This recommendation is made even though it is understood that FQPA and SDWA do not confer on any other agency the regulatory authority to require screening and testing for endocrine disruption potential.